REMARKS and REQUEST FOR CONSIDERATION

Claims 1-23 are currently pending in the application, Claims 14-22 being cancelled in the instant response. Claims 5-6 amd 8-11 have been withdrawn by the Examiner as being drawn to a non-elected species. Claims 1-4, 7, 12 and 13 have been examined on the merits.

Claim 12 is newly amended. The amendment finds support in the specification and is discussed in the relevant sections below. No new matter is added.

Claim Rejections-35 USC § 112, First Paragraph

Written Description

Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The Office action asserts that the "broad limitation of "**about 3 A**" (emphasis added) has not been found in the instant specification" and that the instant specification "discloses the crystal of T. thermophilus having a determined resolution at **3.0 A** (page 30, line 15)" .

Applicants contend that one of skill would consider that determining the resolution of a of T. thermophilus crystal at 3.0 as "about 3 A," in light of the instant disclosure. First, the second sentence of the Abstract of the instant disclosure states: "An advantageous feature of the structure is that it diffracts at ***about 3 A*** resolution", (emphasis added).

Second, the specification of the instant disclosure discusses the variability in the crystal structure of T. thermophilus, reproduced in part below:

> "The high resolution structure provided herein provides a crystal with unit cell dimensions which are provided in the accompanying table to 3 decimal places, as set out above. However, those of skill in the art wishing to reproduce the crystallization described herein and obtain such crystals ***will appreciate that a degree of experimental variability and error will mean that crystals of the invention will be obtained with a unit cell dimension within, but not exactly corresponding to, this size.*** Thus crystals of the invention may generally be defined as having unit cell dimensions a, b, and c as defined above which vary ..... More preferably the variance is ..... no more than a .+-. about 0.2 A., b .+-. about 0.2 A. and c .+-. about 0.4 A. These unit cell sizes are believed to define

> novel and more highly resolved unit cell sizes than has previously been possible in the art." (emphasis added) (page 12 line 10-25).

In view of the instant disclosure of the art-recognized variability in unit cell sizes in crystal structure, and in view of the Abstract's characterization of the crystals of the invention as being about 3 A, Applicants contend that the recitation of a crystal structure of "about 3 A" is not new matter. Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Enablement

The Office Action maintains the rejection of Claims 1-4, 7, 12 and 13 under 35 U.S.C. 112, first paragraph, enablement, because "the specification, while being enabling for a crystal structure of the *Thermus thermophilus* 30S subunit, does not reasonably provide enablement for any 30S subunit".

The Office Action acknowledges, but does not comment on, Applicants' previous traversal that the support provided in the specification is not limited to a crystal structure of the *Thermus thermophilus* 30S subunit, but provides support for a crystal structure of prokaryotic 30S subunits. This support is based on the property of structural conservation of ribosomes, as evidenced by the following excerpt from page 11 of the specification:

> "This methodology provides those of skill in the art a means to provide 30S crystals of T.thermophilus. **The conservation of ribosome structure, particularly regions of structure essential for function, between prokaryotes, for example prokaryotes which are human pathogens, such as Staphylococcus spp, and the like, allows the structure herein to be useful in the provision of anti-bacterial agents in general.** Thus, the structure may be used to solve 30S subunits by the technique of molecular replacement. In such a method, x-ray diffraction data are obtained from crystals of a 30S subunit from another species, e.g. a species of a bacteria pathogenic to humans. The coordinates of Table 1 may be used to find the orientation of the unknown molecule in the crystal, and electron density maps calculated. **These maps can then be interpreted with the sequence of the species in question, and the coordinates of our 30S structure can be used to help and speed interpretation.** In this way, the structure of our 30S facilitates the determination of structures of 30S subunits and whole ribosomes from other organisms.
>
> **Accordingly, the invention provides a method for the determination of the structure of a bacterial 30S from a species other than T. thermophilus.**" (emphasis added).

This excerpt from the specification clearly demonstrates that the specification discloses guidance for making crystals of 30S subunit from different species based on the property of structural conservation of ribosomes.

However, the Office Action does not comment on the above disclosure, but merely asserts the rejection by stating:

> "It is noted that the cited disclosure provides a description of means for providing crystals of *T. Thermophilus* as exemplified by Examples 1-4 (pages 22-34) that are specific for *T. Thermophilus*. However, Applicant does not disclose ***by guidance or working example*** for making crystals for different species based on the property of structural conservation of ribosomes. Therefore one of skill in the art would not know how to predictably practice the claimed invention based on structural conservation of ribosomes without undue experimentation" (emphasis added).

Despite the absence from the instant specification of working examples directed to crystals of 30S subunits from other prokaryotic species, Applicants contend that the specification ***does provide guidance*** for making crystals of 30S subunits from prokaryotic species other than T.thermophilus, based on the property of structural conservation of ribosomes, as discussed above.

Applicants' crystallization for the first time of a 30S *T. Thermophilus* ribosomal subunit to the 3A resolution, paves the way for the crystallization to the 3A resolution of a 30S ribosomal subunit from other prokaryotic species. The specification provides that the technique of molecular replacement can use the coordinates of the 30S *T. Thermophilus* ribosomal subunit of the instant invention to help and speed the interpretation of data from crystals of a 30S subunit from other prokaryotic species, by virtue of the structural conservation among prokaryotic 30S ribosomal subunits. Accordingly, the 3A resolution structure of the instant invention disclosed in the instant specification, can be used to facilitate the determination of structures of 30S subunits from prokaryotic organisms other than *T. Thermophilus*.

Applicants note that a disclosure is presumed to be enabling, In re Cortright, 165 F.3d 1353, 1356-57, 49 USPQ2d 1464, 1466 (Fed. Cir. 1999), absent some clear indication to the contrary, id. at 1360, 49 USPQ2d at 1469. But none the less, the office action concludes that: "Therefore one of skill in the art would not know how to predictably practice the claimed invention based on structural conservation of ribosomes without undue experimentation." This conclusion is improperly based on conjecture.

No clear, objective evidence to the contrary has been provided for putative lack of enablement for making crystals of ***30S subunits*** from prokaryotic species. The Office Action restates and maintains its conclusion that because the crystallization of an individual ***protein*** is unpredictable, the crystallization of a subunit comprising a multitude of proteins is unpredictable. Specifically the Office Action states that:

> "As concurred by Applicant, the art of crystallizing individual proteins is unpredictable. It is reasonable to expect that it would be unpredictable at best to reproduce crystals of individual proteins due to the high failure rate for proteins that are being crystallized. Applicant discloses that the 30S subunit comprises 16S RNA and 20 associated proteins. The increase in number and complexity (20 associated proteins and 16S RNA) of the protein to be crystallized would increase the unpredictability factor, which would result in even higher failure rate for the 30S subunit proteins that are being crystallized." (emphasis added)

However, the Office Action *provides no objective basis* for making the leap from applying the degree of unpredictability inherent in crystallizing any number of individual proteins of widely differing physical characteristics, to the degree of unpredictability in crystallizing 30S ribosomal subunits which have a highly ordered structure that is conserved among prokaryotic species.

Applicant notes that the evidence of record is directed to protein crystallization. Further Applicant notes that lack of "evidence of record" that pertains to crystallization of ribosomal 30S subunits. Applicant contends that in order to properly maintain this rejection, *the evidence of record must be based on prokaryotic 30S ribosomal subunit crystallization and not individual protein crystallization.*

Although it may be unpredictable to crystallize individual proteins for the reasons stated above in the office action, Applicant notes that a crystal of an individual protein is not being claimed. Rather a crystal of a 30S ribosomal subunit is being claimed. The office action does not state why the principles of unpredictability in crystallizing a protein would apply to the unpredictability of a 30S ribosomal subunit. In contrast to researchers having trouble generating sufficient individual proteins required for the crystallization process, generating sufficient prokaryotic ribosomes for crystallization has not historically been troublesome, due to their

abundance in prokaryotic cells and due to the ease of ribosomal purification from prokaryotic cultures. Unlike individual proteins, prokaryotic 30S ribosomal subunits have a defined conserved structure. Therefore, the validity of the Office Action's assertions that the unpredictability of crystallizing a protein applies to the crystallization of a large unit as a 30S ribosomal subunit is not clear.

Further, In fact, Applicants note that the first crystallization of a ribosomal subunit was over twenty years ago (Yonath et al. (1980) Biochem Int. 1, 428-435). Further Applicant notes that ribosomal subunits from several different species have been crystallized, as evidenced by Clemons et al (J. Mol. Biol. (2001):310:827-843, cited in IDS) which includes publications by Cate et al., (1999), Ban et al., (1999), Clemons et al., (1999), and Tocilj et al., (1999). In view of the many instances of ribosomal subunit crystallization over the years, it does not appear that there is a high failure rate for crystallization of ribosomal subunits, absent evidence to the contrary. In fact, Clemons teaches on pages 834-835 that 30S subunit crystals diffract well and that "the crystal form of the 30S subunit mimics a ligand bound state, which is probably responsible for its conformational homogeneity and the resulting diffraction to high resolution".

In view of Applicant's arguments detailed above and in view of the specification's teaching of the applicability of the disclosed crystallization methods to 30S ribosomal subunit from any prokaryotic species, Applicant respectfully submits that the office action has not met its burden in demonstrating that the specification is not enabling for the crystallization of a prokaryotic 30S ribosomal subunit.

In view of the amendment to claim 12, and in view of the above mentioned arguments, Applicant respectfully requests reconsideration and withdrawal of this rejection on the grounds that the instant specification clearly discloses how to make and use a crystal of a prokaryotic 30S subunit as instantly claimed.

Double Patenting

Claims 1-4, 7, 12 and 13 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of copending Application No. 09/904,779, in view of Ramakrishnan et al.

Upon indication of allowable subject matter, a terminal disclaimer will be filed.

Conclusion

Applicants submit that in view of the foregoing remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicants respectfully request the withdrawal of rejections over the claims of the present invention. Upon the indication of allowable claims, Applicants respectfully request rejoinder and examination of withdrawn claims 5-6 and 8-11, which were withdrawn by the examiner as being drawn to a nonelected species.

Respectfully submitted,

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